BCL6 enables Ph(+) acute lymphoblastic leukaemia cells to survive BCR-ABL1 kinase inhibition.

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Public Summary:
Tyrosine kinase inhibitors (TKIs) are widely used to treat patients with leukaemia driven by BCR-ABL1 (ref. 1) and other oncogenic tyrosine kinases. Recent efforts have focused on developing more potent TKIs that also inhibit mutant tyrosine kinases. However, even effective TKIs typically fail to eradicate leukaemia-initiating cells (LICs), which often cause recurrence of leukaemia after initially successful treatment. Here we report the discovery of a novel mechanism of drug resistance, which is based on protective feedback signalling of leukaemia cells in response to treatment with TKI. We identify BCL6 as a central component of this drug-resistance pathway and demonstrate that targeted inhibition of BCL6 leads to eradication of drug-resistant and leukaemia-initiating subclones.

Scientific Abstract:
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